INPLASY PROTOCOL

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Support: **Not applicable.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a meta-analysis of propensity-score matched studies

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Review question / Objective: **We aim to perform the first meta-analysis of propensity-score matched (PSM) studies to compare the short- and long-term outcomes of LLR versus OLR for HCC in elderly patients.**
Eligibility criteria: **The inclusion criteria were as follows: 1. Population: elderly patients (≥65 years old) with pathology-confirmed HCC; 2. Intervention: laparoscopic surgery for liver resection; 3. Comparison: open surgery for liver resection; 4. Outcomes: short-term outcomes including postoperative morbidity, surgical time, blood losses, and length of hospital stay. Long-term outcomes including 1-, 3- and 5-year overall survival (OS) rate, 1-, 3- and 5-year disease-free survival (DFS) rate. 5. Design: PSM.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 April 2022 and was last updated on 27 April 2022 (registration number INPLASY202240155).

INTRODUCTION

Review question / Objective: **We aim to perform the first meta-analysis of propensity-score matched (PSM) studies to compare the short- and long-term outcomes of LLR versus OLR for HCC in elderly patients**

Condition being studied: **Liver cancer is one of the most common cancers and a main global health challenge. According to the GLOBOCAN 2020, liver cancer is the seventh most common malignancy and the fourth leading cause of cancer death, causing an estimated 830,180 deaths in 2020 globally. Hepatocellular carcinoma (HCC) represents about 90% of primary**

liver cancers and constitutes a major health problem worldwide. Since Reich et al. reported the first laparoscopic liver resection (LLR) at 1991, this minimally invasive technique has advanced continuously. Nowadays, this minimally invasive technique has gained increasing acceptance for surgical treatment of HCC. With the advancement of laparoscopic techniques, surgeons gradually preferred a laparoscopic approach rather than traditional open liver resection (OLR) for some major well-known advantages such as less postoperative pain and complications, faster recovery, shorter length of hospital stay, and better quality of life. However, some parameters such as the presence of significant comorbidities or age may have a critical impact on the safety profile and efficacy of this minimally invasive technique. Age is a challenging feature given the significant heterogeneity of general conditions among individuals of the same age range and the growing number of elderly patients in good clinical condition presenting with HCC. Also, elder patients are seldom included in randomized clinical trials, resulting in a lack of knowledge about the benefit/risk ratio of treatment strategies. These factors lead clinicians to constantly refine the boundaries of treatment indications. Furthermore, to surmount selection and confounding biases inherent in most non-randomized studies, we elected to limit to studies which performed propensity-score matched (PSM), because a large body of statistical literature and meta-epidemiological studies have shown that PSM studies are empirically equivalent to RCTs in their ability to derive unbiased estimates. Therefore, in order to summarize the current high-quality evidences, we performed the first meta-analysis of PSM studies to compared the short- and long-term outcomes of LLR versus OLR for the treatment of HCC in elderly patients.

METHODS

Search strategy: #1 Liver Neoplasms [MeSH] OR Carcinoma, Hepatocellular [MeSH] OR liver cancer [Title/Abstract] OR hepatoma [Title/Abstract] OR Hepatic carcinoma [Title/Abstract] OR liver carcinoma [Title/Abstract] OR hepatocellular carcinoma [Title/Abstract] OR hepatic cancer [Title/Abstract]
#2 Laparoscopic [Title/Abstract] OR Laparoscopy [MeSH] OR Laparoscopy [Title/Abstract]
#3 open [Title/Abstract]
#4 PSM [Title/Abstract] OR propensity score [Title/Abstract]
#5 Aged [MeSH] OR Elderly [Title/Abstract] OR older [Title/Abstract]
#1 AND #2 AND #3 AND #4 AND #5.

Participant or population: Population: elderly patients (≥65 years old) with pathology-confirmed HCC.

Intervention: Intervention: laparoscopic surgery for liver resection.

Comparator: Comparison: open surgery for liver resection.

Study designs to be included: propensity-score matched study.

Eligibility criteria: The inclusion criteria were as follows: 1. Population: elderly patients (≥65 years old) with pathology-confirmed HCC; 2. Intervention: laparoscopic surgery for liver resection; 3. Comparison: open surgery for liver resection; 4. Outcomes: short-term outcomes including postoperative morbidity, surgical time, blood losses, and length of hospital stay. Long-term outcomes including 1-, 3- and 5-year overall survival (OS) rate, 1-, 3- and 5-year disease-free survival (DFS) rate. 5. Design: PSM.

Information sources: A literature search was performed in PubMed, Embase, Scopus, and Cochrane Library for eligible RCTs in English from inception through April 2022.

Main outcome(s): Outcomes: short-term outcomes including postoperative morbidity, surgical time, blood losses, and length of hospital stay. Long-term outcomes including 1-, 3- and 5-year

overall survival (OS) rate, 1-, 3- and 5-year disease-free survival (DFS) rate.

Quality assessment / Risk of bias analysis: Two authors (G.Y. and S.W.) independently assessed the methodological quality of including studies by using the Newcastle-Ottawa Scale for cohort studies. The Newcastle-Ottawa Scale contains three categories (including 8 subcategories), and a maximum of 9 stars can be allotted to each study. A score of 0 to 3 stars was considered a low-quality study, a score of 4 to 6 stars was considered a moderate-quality study, and a score of 7 to 9 stars was considered a high-quality study.

Strategy of data synthesis: For short-term outcomes, we combined data from included studies to estimate the pooled odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes, and continuous outcomes were pooled as mean difference (MD) with 95% CI. The meta-analysis of OS and DFS used the hazard ratio (HR) with 95% CI reported in the primary studies. If the primary studies did not provide the HR data, we obtained the HR data by digitizing the Kaplan-Meier survival curves. The heterogeneity between studies was tested by the Chi-squared test with significance set at P value of 0.1, and quantitatively by inconsistency (I2) statistics. Substantial heterogeneity was identified when I2 value>30% and we employed a random-effects model to perform the analysis, otherwise a fixed-effects model would be used. In addition, we used the funnel plot and Egger¡¯s regression test to assess the publication bias.

Subgroup analysis: A predefined subgroup analysis was stratified by types of hepatectomy (major versus minor hepatectomy,) to investigate the potential source of heterogeneity.

Sensitivity analysis: We performed a sensitivity analysis to explore the effect of individual study by omitting each one at a time.

Language: English.

Country(ies) involved: China.

Keywords: Hepatocellular carcinoma; Laparoscopic liver resection; Open liver resection; Meta-analysis; Elderly.

Contributions of each author:
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